REMARKS

Applicants' representatives wish to thank the examiner for courtesies extended during the personal interview held on June 4, 2002. These remarks address the concerns voiced by the examiner and discussed during the interview.

Claims 13-15, 17-24 and 37-38 are pending. Applicants respectfully request reconsideration of these claims in view the following comments

I. Rejection of Claims 13-15 and 17-24 under §101

The examiner has maintained a rejection of claims 13-15 and 17-24 for the lack of credible or a well-established utility. Previously, the examiner has asserted that no credible utility for administering to a human active cell is established because (1) all examples of the instant specification, using well-characterized murine tumor models, involve administering tumor cells that were first irradiated and (2) human tumors are poorly immunogenic, unlike the murine tumor cell lines used in the examples.

Thus, the utility rejection apparently derives from the examiner's doubts as to the safety of administering an active tumor to human and efficacy of co-culture products comprising a human tumor. Consideration of safety and/or degree of effectiveness is not required, however, to show credible and well-established utility. See MPEP 2107.03, V.

A utility taught in a patent specification is "credible," under Section 101, unless (a) the logic underlying the assertion is seriously flawed or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. In this context, the credibility of a given utility is gauged from the perspective of whether a person of ordinary skill would consider it credible in view of "contemporary knowledge." The specific assertion of a particular utility for a claimed invention cannot be dismissed out of hand, even when there may be reasons to believe that the assertion is not entirely accurate.

In the present case, the Office has not considered contemporary knowledge in the area of cancer immunotherapy and, hence, has not shouldered its burden with respect to the credibility determination, as discussed above.

Tumor vaccines, employing autologous or syngeneic tumor cells, have been used to generate an active, tumor-specific immune response, as evidenced by review article of Schirmacher *et al.*, *J. Cancer Res. Clin.Oncol.* 121:487-89 (1995) (copy appended). It is apparent from the Schirmacher review that the use of irradiated or inactivated tumor cells in tumor vaccines is common in this area. *See* page 487 in the right column, first full paragraph, and page 488 in the right column, last paragraph.

That using irradiated or inactivated tumors in tumor vaccines was part of the relevant contemporary knowledge is substantiated as well by U.S. patent No. 6,277,368 B1 ("the '368 patent") (copy appended). More specifically, the '368 patent teaches a cellular vaccine composition comprised of cancer cells and other components, such as a tumor-associated antigen or a cytokine expressing cell line. (Cancer cells or cell lines may be used as a tumor-associated antigen.) The '368 patent states that cancer cells in this composition optionally or preferably are inactivated, to prevent further proliferation after they are administered to a subject. An inactivation methodology also is described, *e.g.*, at column 11, last full paragraph, at column 12, third full paragraph, and at column 15, first full paragraph.

Accordingly, the use of inactivated (irradiated) cancer cells in tumor vaccines was common knowledge and well understood among persons skilled in the art when applicants filed their application. With this consensus as background, claim 9 of the '368 patent, which is directed to a immunogenic composition comprising autologous tumor cells, was allowed without a recited "inactivation," or words to this effect.

As indicated by the examiner, applicants' working examples comport with this common knowledge, in that they illustrate the use of pre-administration irradiation (see Examples 4 and 5). Reading the present specification, a skilled person with the conventional knowledge in the area of tumor vaccines surely would understand that, when administered to a subject, the claimed composition is subjected to the inactivation of active tumor cells, as needed, and thus would not doubt the credible utility of the claimed composition. Indeed, it is the examiner's burden to show the contrary, using objective evidence that applicants' asserted utility is incredible. Applicants respectfully submit that there is no such evidence of record, which is reason enough for the examiner to withdraw the "lack-of-utility" rejection under Section 101.

Another reason proffered by the Office for the pending utility rejection derives from the doubt of efficacy of the claimed composition when using human tumor cells that are less immunogenic than murine tumor cells. However, the concern expressed in this regard is not relevant in the claimed composition because it does not use tumor cells alone. Rather, the claimed composition comprises co-culture products of tumor cells with dendritic cells ("DCs"). DCs are believed to be potent antigen-presenting cells that can promote recruitment, activation or stimulation of the interaction of host immune cells, resulting in an enhanced immunological response.

Whether human tumor cells alone are less immunogenic therefore is not relevant vis-à-vis the utility of the claimed co-culture products of tumor cells and DCs. This fact alone militates in favor of a withdrawal of the utility rejection. Still, applicants would explain further why the evidence of record is insufficient to case doubt or otherwise detract from applicants' statement of utility.

The examiner attempts to cast doubt on the credibility of treating human tumors, in accordance with the present invention, by citing Fenton *et al.*, *J. Nat'l Cancer Inst.* 87(4): 241-43 (1995) for the proposition that human tumors are poorly immunogenic. Yet the Fenton publication also mentions that "several findings in patients during the last 3 years with melanoma have given rise to optimism that at least some tumor types may be susceptible to immune attack" (left column, lines 11-13). Thus, Fenton actually bolsters rather than detracts from the prospect of treating at least some tumor types, pursuant to applicants' teaching.

In the context of speculating on how a clonally heterogeneous mixture of tumor cells escape killing, Fenton *et al.* does suggest that a heterogeneity of class I MHC expression within a tumor-cell population, resulting in antigen-processing defects, may constitute a significant obstacle to antigen-specific T-cell therapy. What the Fenton article questions in this regard, however, is whether *in vivo* administration of interferon gamma may influence class I MHC expression in a proportion of patients.

This emphasis in Fenton, an article published some two years before the priority date of the present application, should not obscure the fact that the present invention takes into account the possibility that, in some instances, mature dendritic cells ("DCs")

from a tumor-bearing host have defects in antigen presenting cell ("APC") function, and also that human cancer cell can release soluble factors that can inhibit the maturation of dendritic cells. In light of these potential obstacles, the inventors conceived of using DCs in co-culture with tumor cells, thereby to circumvent the tumor-induced APC dysfunction that, in a somewhat different context, was the focus of Fenton *et al.* Accordingly, the Fenton publication does not substantiate a reasonable doubt over the stated utility of applicants' claimed invention, ***which itself addresses the concern of Fenton***.

The examiner also questions applicants' stated utility by asserting that test data in the specification are from experiments that employed "highly immunogenic," murine tumor cell lines. Yet, in adjudging whether *in vitro* data or animal tests support an asserted utility, the examiner should gauge whether a skilled person would view the data as reasonably predictive of the asserted utility. MPEP 2107.03, III, page 2100-44.

On this point, applicants would emphasize again that the claimed composition employs DC/tumor-cell co-culture, not tumor cells alone. As explained above, the use of DC not only boosts immunogenecity in DC/tumor-cell co-culture vaccines but also compensates the impact of poor immunogenic tumor cells on inducing immune response.

Moreover, the appended publication of Celluzzi *et al.*, *J. Immunol.* 1998: 1, evidences an understanding in the art that data obtained from murine DC/tumor-cell co-culture vaccines are indicative of the immunotherapeutic effects of human DC/tumor-cell; this, because human DCs are phenotypically and functionally similar to the murine DCs. This understanding also has been validated by human test data published by Kugler *et al.*, *Nature Medicine* 6: 332-336 (2000). More specifically, Kugler *et al.* present a human vaccination study that employed a DC/tumor-cell hybrid, and the authors conclude that hybrid-cell vaccination is effective therapy for human metastatic renal cell carcinoma. See page 332, left column, lines 19-22 and page 335, left column, second full paragraph.

Accordingly, the evidence of record supports the proposition that a person skilled in immunotherapy would accept applicants' murine-model test data as being reasonably

predictive of an application humans and, hence, as supporting the credibility of the asserted utility. Conversely, the examiner has not marshaled convincing evidence or explanation as to why a skilled person would disbelieve the utility of the claimed invention, notwithstanding the state of contemporary knowledge after Fenton (1995). Even with Fenton, therefore, the examiner has not carried his burden to rebut the presumption of credibility that attaches to applicants' teaching of utility for the claimed invention.

II. Rejection of claims 13-15 and 17-24 under 35 USC §112, first paragraph

The examiner also has rejected claims 13-15 and 17-24, asserting lack of enabling disclosure. The rationale for this "non-enablement" rejection under Section 112 appears to be the same as that for the above-discussed "lack of utility" rejection under Section 101. Because the latter rejection is ill-conceived, for the reasons detailed above, applicants submit that the accompanying non-enablement rejection likewise should not be maintained. Accordingly, reconsideration and withdrawal of both rejections are requested.

III. Rejection of claims 37-38 under 35 USC §112, first paragraph

The examiner has rejected claims 37 and 38 for the lack of written description. The examiner asserts that although applicants indicated that the example at pages 13-14 of the specification supports the irradiation of co-culture products before administration, (1) said examples disclose only hybridoma that is a non-elected invention, and (2) said disclosure is insufficient description of the claimed genus. Applicants respectfully traverse this rejection.

With respect to reason (1), applicants would like to direct the examiner's attention to Examples 4 and 5 (at pages 13-14 and 16), which specifically disclose irradiation of co-culture before administration.

Satisfactory disclosure of a "representative number" of species with the claimed genus depends on whether one skilled in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus. Only when there is substantial variation within the genus

must one describe a sufficient variety of species to reflect the variation within the genus. However, one species may supports a genus. See MPEP 2163 II-A-3-ii).

The examiner does not provide any evidence that there is likely to be substantial variation among the species within the genus of "irradiation of co-culture before administration," if any. Furthermore, as explained above, "irradiation or inactivation" of tumor cells in vaccines before its administration, is well-known technology generally applied to any tumor vaccines. Absent contravening objective evidence, therefore, the written description requirement for a claimed invention should be satisfied through the description of actual reduction to practice of one species that is representative of the claimed genus, as already demonstrated in Examples 4 and 5. Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

In view of the foregoing, applicants submit that the present application is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The examiner is invited to contact the undersigned by telephone, should he feel that any other issue requires consideration.

Respectfully submitted,

Date 12 July 2002 By S. A. Bent

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768